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EXAMINER	
POPA, ILEANA	
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1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efspatents@sbiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/652,814	UNGER, GRETCHEN M.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-95,97-100,102-109,111-116,118,119,122-124,126,127, and 133-141* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,67,87-94 and 133-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/15/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 68-86,95,97-100,102-109,111-116,118,119,122-124,126 and 127.

DETAILED ACTION

1. Claims 1-65, 96, 101, 110, 117, 120, 121, 125, and 128-132 have been cancelled. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 have been withdrawn. Claim 66 has been amended.

Claims 66, 67, 87-94, and 133-141 are under examination.

2. Upon further considerations, the following rejections are withdrawn in favor of new rejections using secondary references which provide a better motivation to arrive at the claimed invention:

The rejection of claims 66, 67, 87-94, and 135-139 under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US Patent No. 6,139,819), in view of each Kondo et al., Medina (U.S. Patent No. 5,650,543), Quay (U.S. Patent No. 5,707,606), and Duquemin et al. (J Pharm Pharmacol, 1985, 37: 698-702, Abstract);

The rejection of claims 66, 67, 87-94, and 133-141 under 35 U.S.C. 103(a) as being unpatentable over Unger et al. taken with each Kondo et al., Medina, Quay, and Duquemin et al., in further view of Schneider et al. (FEBS Letters, 1998, 429: 269-273).

Specification

3. The disclosure remains objected to for the use of the trademarks Qiaquik, Zymoclean, Synergel, SybrGold, and Storm 860 (p. 23, lines 20-25). The trademarks

should be capitalized wherever they appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 11 of copending Application No. 12/027,863. Although the conflicting

claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that the instant rejection has not been previously presented because Application No. 12/027,863 was filed on 02/07/2008, which is after the mailing date of the non-final Office action of 12/11/2007. It is also noted that Application No. 12/027,863 is a continuation of Application No. 10/958,999 and that claims 8 and 11 of Application No. 12/027,863 are identical to claims 10 and 13 of the abandoned Application No. 10/958,999. Therefore, the instant rejection is the same as the obviousness-type double patenting rejection previously made over claims 10 and 13 of Application No. 10/958,999 (see the non-final Office action of 12/11/2007).

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139), which can be associated with a nucleic acid

condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136. The specification defines that the polynucleotide could be an anti-sense DNA (p. 23, line 1).

The application claims recite a collection of particles comprising an agent, a surfactant molecule having an HLB of less than 6.0, a polymer soluble in aqueous solution, wherein the collection of particles has an average diameter of less than about 100 nm as measured by atomic force microscopy after drying and wherein the agent is an anti-sense nucleic acid (claim 8). The collection of particles further comprises a cell recognition agent (claim 11). The specification defines that the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol, as recited in the instant claims 87, 88, 90, and 136 (i.e., a surfactant with an HLB of less that 5.0), the particles further comprise Li^+, wherein Li^+ is used to precipitate the biocompatible polymer that surrounds the micelles comprising the surfactant and bioactive agent, and the polymer can be tenascin (p. 8, lines 8 and 9, p. 12, lines 8-23, p. 17-18, Table 1, p. 56, lines 5 and 6). With respect to the limitation of nanocapsule, the specification defines that the particles can be formulated as nanocapsules (p. 13, lines 8 and 9). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, one of skill in the art would know to do this because the art teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims and the instant claims are obvious variants of one another.

6. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25-28 of copending Application No. 11/622,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136.

The application claims drawn a collection of particles having a bioactive component, a surfactant with an HLB less than 6.0, a biocompatible polymer, and a cell recognition component having affinity for a cell receptor; the average diameter of the

particles is less than 50 nm as measured by atomic force microscopy after drying of the particles (claim 25), wherein the bioactive component is a polynucleic acid (claim 28) and wherein the biocompatible polymer is tenascin claims 26 and 27). The specification defines that: **(i)** the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (i.e., a surfactant that has an HLB of less than 5.0, as recited in the instant claims 87, 88, 90, and 136), **(ii)** the particles comprise surfactant micelles containing surfactant and a bioactive agent, **(iii)** the biocompatible polymer forms a shell surrounding the surfactant micelles, and **(iv)** the biocompatible polymer is precipitated by cations such as Li^+ (p. 9. lines 21-23. p. 10, lines 1-21, p. 75, lines 15-18, p. 76, lines 3-13). With respect to the limitation of nanocapsule, the specification disclosed that the particles can be formulated as nanocapsules (p. 11, lines 6 and 7). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing agents are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims and the instant claims are obvious variants of one another.

7. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and

a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88), the surfactant can be non-ionic (claim 87) or is selected from the group recited in claims 90 and 136, the composition further comprises a water-miscible solvent (claim 93).

The patent claims recite a plurality of particles comprising a surfactant with an HLB less than 5.0, a bioactive hydrophobic component (i.e., a bioactive component), and a biocompatible polymer, wherein the particles have an average diameter of less than 50 nm as determined by atomic force microscopy and wherein the biocompatible polymer is precipitated in the presence of a cation (claims 29, 37, and 42). The surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (claim 33), as recited in the instant claims 87, 90, and 136, and the particles further comprise a water-miscible solvent (claim 31). With respect to the limitation of the biocompatible polymer providing specific cellular uptake, the specification discloses that the biocompatible polymer can be tenascin (see fig. 7B, and also column 3, lines 6-8). The specification discloses that the biocompatible polymer forms a shell surrounding the

surfactant micelles containing the bioactive component and the surfactant, the hydrophobic bioactive component can be a polynucleic acid, and that the precipitating cation is Li^+ (Abstract, column 3, lines 25-32, column 5, lines 37-59, column 7, lines 32-37, column 9, lines 40-45, column 10, lines 42-66, column 15, lines 30-32). With respect to the limitation of HLB being less than 6.0, the patent claims recite an HLB less than 5.0 that anticipates the claimed HLB of less than 6.0. With respect to the limitation of nanocapsules, the specification discloses that the particles are formulated as nanocapsules (Abstract). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Therefore, the patent claims and the instant claims are obvious variants of one another.

The applicant acknowledges the rejections above and notes that they will be addressed when the other issues are resolved. The applicant's comments are acknowledged, however the rejections will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 66, 67, 87-94, and 133-141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over recitation of the phrase 'less than about' preceding the HLB number, the particle size, or the critical micelle concentration (e.g., claims 66, 88, 89, and 139). The term 'less' indicates a maximum value; however, the term is controverted by the term 'about', which implies that values above and below the specified numbers are permitted. Since the instant specification does not define the metes and bounds of the term, the term "less than about" is indefinite. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated:

> "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of 'at least about 160,000' was indefinite".

After review, the CAFC states: "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase 'at least about' indefinite where the metes and bounds of the term were not defined in the specification. Please note that, although the instant claims recite "less" and not "at least", the two terms are equivalent, i.e., they both set forth a value which should not be exceeded; in both cases, this set value is controverted by the term "about".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 66, 67, 87-89, 93, 94, 135, and 137-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueda et al. (J. Microencapsulation, 1997, 14: 593-605), in view of each Landry et al. (Biomaterials, 1996, 17: 715-723), Ghitescu et al. (J. Cell Biol., 1986, 102: 1304-1311), Kondo et al. (Anal Biochem, 1991, 198: 3035, Abstract, of record), and Boulikas (U.S. Patent No. 6,030,956).

Ueda et al. teach nanoparticles comprising: **(i)** a core provided by loperamide (i.e., a bioactive compound having a therapeutic effect) and a surfactant micelle, wherein the surfactant has a HLB less than 5.0; and **(ii)** a surrounding PVA-coated biodegradable polymer shell; the surfactant with a HLB less than 5.0 is Span (i.e., non-ionic and having a critical micelle concentration of less than 200 μM). The nanoparticles further comprise a water-miscible solvent (claims 66, 87-89,93, 135, and 139) (Abstract; paragraph bridging p. 594 and 595; p. 599, second full paragraph; p. 600, Table 4).

Ueda et al. do not teach a shell comprising a polypeptide (claims 66 and 159). Landry et al. teach that nanoparticles formed by the solvent-evaporation technique (such as the one of Ueda et al.) require either PVA or albumin for their production (p. 715, column 2, second full paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ueda et al. by replacing PVA with albumin to achieve the predictable result of obtaining drug-loaded nanoparticles. It is noted that, by doing such, one of skill in the art would have obtained

a nanoparticle having a shell comprising albumin which provides specific cellular uptake by binding to a cell-surface receptor (see Ghitescu et al., Abstract).

Ueda et al. and Landry et al. do not teach precipitating the albumin coat with a cationic precipitating agent such as Li^+ (claims 66, 138, and 139). However, doing such is suggested by the prior art. For example, Ueda et al. teach that a precipitated shell enhances drug entrapment within the nanoparticles (p. 598). Furthermore, using Li^+ to precipitate proteins was routine in the prior art (see Kondo et al., Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ueda et al. and Landry et al. by further precipitating the protein coat with Li^+, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to increase drug entrapment within the nanoparticles. One of skill in the art would have reasonably expected to be successful in doing such because the prior art teaches that Li^+ can be successfully used to precipitate proteins.

Ueda et al., Landry et al., and Kondo et al. do not teach a particle size of 50 nm (claims 66 and 139). However, they do teach that particle size can optimized by varying parameters such as the homogenization conditions, PLA and albumin concentration, or PLA and albumin molecular weight (see Ueda et al., p. 595 and 597; Landry et al., p. 716, column 2, first and second full paragraphs). Furthermore, the prior art teaches the necessity of avoiding the degradation of bioactive agents within lysosomes by using nanoparticles of about 50-60 nm which could be internalized via caveolae (see Boulikas, column 12, lines 45-54). It would have been obvious to one of skill in the art,

at the time the invention was made, to vary the parameters in the method of optimize the size of the nanoparticles of Ueda et al., Landry et al., and Kondo et al. with the purpose of obtaining particles suitable of being delivered inside the cells via caveolae.

With respect to the limitation of the bioactive agent being a polynucleotide (claim 67), it would have been obvious to one of skill in the art to use the particles taught by the combined teachings above in gene therapy, because the prior art teaches the necessity to use gene therapy to treat diseases such as cancer (see Boulikas, Abstract, column 7, line 50 through column 8, line 16, column 10, line 66 and 67). With respect to the limitation of a condensing agent (claim 137), Boulikas teaches using DNA condensing agents such as histones to increase the nuclear import of the polynucleic acid to be expressed within the cell (column 12, lines 45-54). It would have been obvious to one of skill in the art, at the time the invention was made, to further include a histone, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to increase the expression rate of the therapeutic nucleic acid. One of skill in the art would have reasonably expected to be successful in doing such because the prior art teaches the successful use of condensing agents such as histones to deliver nucleic acids to the nucleus.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claims 66, 67, 87-90, 93, 94, 135, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueda et al. taken with each Landry et al., Ghitescu et

al., Kondo et al., and Boulikas, in further view of Krishnan et al. (Colloids Surfaces A: Physicochem. Eng. Aspects, 1999, 149: 355-366).

The teachings of Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas are applied as above for claims 66, 67, 87-89, 93, 94, 135, and 137-139. Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas do not teach acetylenic diols such as 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol (claims 90 and 136). However, using such is suggested by the prior art. For example, Ueda et al. teach that surfactants that an HLB less than 5.0 is necessary for efficient incorporation of hydrophilic therapeutic agents (see, p. 599). Furthermore, 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol was known in the prior art as having an HLB of 3 (see Krishnan et al., Abstract, p. 357, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the nanoparticles of Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas by replacing their surfactant with 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol to achieve the predictable result of efficiently incorporating hydrophilic therapeutic agents such as nucleic acids into nanoparticles.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 66, 67, 87-89, 91-94, 135, and 137-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwata et al. (J. Microencapsulation, 1992, 9: 201-214) in view of each Davies et al. (Journal of Colloid and Interface Science, 1987, 116:

88-99, Abstract), Levy et al. (WO 96/20698), Chang et al. (Journal of Pharmaceutical Sciences, 1996, 85: 13225-1330), and Kondo et al. (Anal Biochem, 1991, 198: 3035, Abstract, of record).

Iwata et al. teach microparticles comprising: **(i)** a surfactant micelle comprising core provided by a drug, wherein the surfactant is Span 80, i.e., a nonioinic surfactant having an HLB of 4.3 (see Davies et al., Abstract) and a critical micelle concentration of less than 200 μM; and **(ii)** a surrounding biodegradable polymer shell. The microparticles further comprise Tween 80, biocompatible oils, and a water-miscible solvent (claims 66, 87-89, 91-93, 135, and 139) (Abstract; paragraph bridging p. 202 and 203; paragraph bridging p. 203 and 204, Fig. 1, Table 1).

Iwata et al. do not teach a shell comprising a polypeptide which provides specific uptake by target cells (claims 66 and 159). Levy et al. teach targeting nanoparticles to specific cells by coating the nanoparticles with polypeptide which provide specific cellular uptake by binding to a cell surface receptor; coating involves freeze-drying to produce a physically-adsorbed coating (Abstract; p. 13, lines 1-7; p. 14, lines 3-9; p. 17, lines 1-9; p. 20, lines 16-20; p. 38, lines 4-8; p. 39, Table 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the microparticles of Iwata et al. by coating them with a polypeptide capable of binding a cell-surface receptor, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the prior art teaches the necessity of localized therapy via sustained drug delivery to cells of interest (see Levy et al., p. 3, lines 9-15). One of skill in the art would have reasonably expected to be successful in

doing such because the prior art teaches that microparticles and nanoparticles can be successfully coated with polypeptides.

Iwata et al. teach microparticles and not nanoparticles having a size of 50 nm (claims 66 and 159). However, Levy et al. teach that the conditions of the solvent-evaporation technique such as the one of Levy et al. could be manipulated to obtain nanoparticles with a size of 20-35 nm (p. 30, lines 4-12; Example 6). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the teachings of Iwata et al. according to Levy et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Levy et al. teach that that these particles are suitable for intravascular administration since, due to their small size, they can easily penetrate the arterial wall and access target tissues (p. 97, lines 11-15).

Iwata et al. and Levy et al. do not teach precipitating the polypeptide coat with a cationic precipitating agent such as Li^+ (claims 66, 138, and 139). However, doing such is suggested by the prior art. For example, Levy et al. teach stabilizing the polypeptide coats by freeze-drying, which induces protein denaturation by precipitation (see Chang et al., Abstract). Furthermore, Li^+ was known in the prior art as a protein precipitating agent (see Kondo et al., Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Iwata et al. and Levy et al. by precipitating the protein coat with Li^+ to achieve the predictable result of producing a physically-adsorbed coating

With respect to the limitation of the bioactive agent being a polynucleotide (claim 67), it would have been obvious to one of skill in the art to use the nanoparticles in gene therapy, because the Levy et al. teach using nanoparticles in gene therapy (p. 10, lines 8-13; p. 12, lines 14-19; p. 110, lines 14-19). With respect to the limitation of a condensing agent (claim 137), it would have been obvious to one of skill in the art to use such because Levy et al. teach using DNA condensing agents such as histones and PLL to protect the polynucleotides from degradation by nucleases (p. 117, lines 6-15).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 66, 67, 87-89, 91-94, 135, and 137-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwata et al. taken with each Davies et al., Levy et al., Chang et al., and Kondo et al., in further view of Schneider et al. (FEBS Letters, 1998, 429: 269-273, of record).

The teachings of Iwata et al., Davies et al., Levy et al., Chang et al., and Kondo et al. are applied as above for claims 66, 67, 87-89, 91-94, 135, and 137-139. Iwata et al., Davies et al., Levy et al., Chang et al., and Kondo et al. do not teach tenascin (claims 133, 134, 140, and 141). Schneider et al. teach identification of a polypeptide derived from the C-terminus of tenascin (claims 133 and 140) capable to bind to $\alpha_9\beta_1$ integrins on the cell surface, i.e., Schneider et al. also teach a ligand that targets a receptor for tenascin (claims 134 and 141) (Abstract, p. 272, column 2 first paragraph

and Fig. 4). Schneider et al. also teach their peptide as being suitable to mediate specific gene delivery to $\alpha_9\beta_1$ integrin-expressing cells (Abstract, p. 269, column 2, second paragraph, p. 272, column 2, second and third paragraphs). It would have been obvious to one of skill in the art, at the time the invention was made to modify the nanoparticles of Iwata et al., Davies et al., Levy et al., Chang et al., and Kondo et al. by coating them with tenascin with the intent to target the particles to $\alpha_9\beta_1$ integrin-expressing cells, with a reasonable expectation of success. The motivation to do so is provided by Schneider et al., who teach that using ligands for $\alpha_9\beta_1$ integrin is promising for the development of targeted gene therapy (Abstract; p. 269). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in making such particles because Iwata et al., Davies et al., Levy et al., Chang et al., and Kondo et al. teach that polypepetides can be successfully used to coat their nanoparticles.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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